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RESEARCH ARTICLE

Incidence of dementia in the German Heinz Nixdorf Recall study over 20 years

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Abstract

INTRODUCTION: The aim of the study was to estimate the population-based dementia incidence in Germany over a period of two decades.

METHODS: We analyzed data from 4814 participants of the population-based Heinz Nixdorf Recall study (49.8% men, 45–75 years at baseline period 2000–2003), who have been monitored for the occurrence of cognitive decline and dementia. We calculated the cumulative incidence of dementia and its major subtypes and the incidence rate per 1000 person-years over two decades.

RESULTS: During a median follow-up of 18.2 (Q1–Q3: 11.3–20.6) years, a total of 298 participants (6.2%) developed dementia (22.1% Alzheimer´s disease, 23.5% vascular dementia, 15.1% mixed dementia, 9.1% other dementia, 30.2% unspecified). The overall incidence rate was 3.9 per 1000 person-years.

DISCUSSION: Our study is the only current population-based study in Germany that estimates the incidence of dementia. In order to reduce the high proportion of unspecific dementia diagnoses, diagnostics urgently need to be improved.

KEYWORDS
Alzheimer´s disease, cohort study, dementia, epidemiology, Heinz Nixdorf Recall study, incidence, incidence rate, mixed dementia, vascular dementia

Highlights

- New data on the incidence of dementia in Germany in participants ≥45 years of age.
- Participants have been monitored for dementia incidence over two decades.
- The overall incidence in our cohort was 3.9 per 1000 person-years.
- Many patients had unspecific dementia diagnoses in their medical records.
- Further diagnostic evaluation should be available for all dementia patients.

1 | BACKGROUND

Advanced health care and public health prevention strategies have led to increased life expectancy in developed nel of the HNR study center and lifetime risk of age-related dementia.[1] Dementia is the most common cause of care dependency in older people worldwide.[1] It is associated with a progressive loss of cognitive function including memory, thinking, orientation, comprehension, calculation, learning, language, calculation, speech, and judgment.[2] In addition, there are usually changes in emotional control, social behavior, or motivation.[2] Consciousness is not impaired.[2] The spectrum of impairments in patients with dementia patients from impairments in daily life functions to the need for around-the-clock care. Dementia has several causes.[2] Alzheimer's disease dementia (AD) is the most common cause. It accounts for an estimated 60%–80% of dementia cases.[3,4] Patients ≥65 years of age survive about 4–8 years after a diagnosis of AD.[4] Other dementia causes include cerebrovascular disease leading to vascular dementia (VaD), combined neurodegenerative and VaD (mixed dementia [MD], frontotemporal dementia [FTD]), Lewy body dementia (LBD), Parkinson's disease (PD) dementia, and other or not further specified dementia causes. The optimal care and social participation of patients with dementia pose high demands on health care systems and society.[5] Therefore, representative national quantitative estimates of dementia incidence are essential for health care system planning. Germany does not have a nationwide dementia register and hence currently lacks representative data on dementia incidence in the general population. Large cohort studies such as the population-based Heinz Nixdorf Recall (HNR) study[6] are needed to inform dementia incidence.

The aim of our study was to identify incident dementia cases in the HNR study and to investigate the age- and sex-specific dementia incidence and its major subtypes over two decades.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using PubMed. Previous studies on dementia incidence in Europe and the United States showed heterogeneous results and mostly reported incidence rates for participants ≥65 years of age. Relevant citations are appropriately cited.
2. **Interpretation**: The study is the only current population-based study in Germany that estimates the incidence of dementia. The estimates are representative of the middle-aged and elderly German population and are comparable to those of previous studies in Europe and the United States. Although Germany has an excellent health care system, two-thirds of individuals identified with dementia had most likely not received any in-depth dementia evaluation using established biomarker assessments according to their medical records.
3. **Future directions**: Dementia is a major health burden. The implementation of accurate and early diagnosis using all available medical options needs improvement to reduce the high proportion of unspecific dementia, even in high-income countries such as Germany.

2 | METHODS

2.1 | Study population and study design

The initial aim of the HNR study was to evaluate the predictive value of coronary calcification using electron beam computed tomography (CT) for myocardial infarction and cardiac death besides traditional cardiovascular risk factors.[6] Briefly, 4814 participants 45–75 years of age were included in the baseline examination (T0, 2000–2003), with a recruitment rate of 55.8%.[7] Participants were invited for follow-up examinations 5 years (T1: $n = 4157$, 2005–2008) and 10 years later (T2: $n = 3087$, 2010–2015). Figure 1 shows the flow chart of the study population. A standardized cognitive performance assessment was conducted at T1 and T2 (see Section 2.2). Genotyping of apolipoprotein E (*APOE*) was performed for all participants.[8] Participants completed annual postal questionnaires on health status. The questionnaires assessed morbidity status, that is, hospital admissions and outpatient diagnoses of neurological and cardiac disease. The yearly response ranged from 88%–95%. The postal follow-up is still ongoing. By a trained follow-up team of one study nurse and six medical students (third to fifth year of medical school) under the supervision of a medical doctor and epidemiologist, questionnaires were screened for possible dementia endpoints (and other endpoints: cardiac disease, stroke, cancer). Further medical information and death certificates were requested. Dementia endpoints were pre-validated by the follow-up team. Finally, documents were presented to an endpoint committee with dementia experts (one neurologist, two psychologists, two epidemiologists), who did the final validation (Supplemental Material (SM) SM1). The HNR study was approved by the ethics committee of the faculty of medicine of the University Duisburg-Essen and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its amendments or comparable ethical standards. All participants provided written informed consent.

2.2 | Assessment of cognitive performance

A standardized cognitive performance assessment was introduced at T1 and extended for T2. In brief, subjective cognitive decline (SCD) was assessed at T1 and T2 with the question: "In comparison to 2 years ago, would you rate your memory function as better, same, or worse?" SCD was defined as present if the participant's answer was "worse." Participants responding "better" or "same" were defined as not having SCD. In addition, cognitive performance at T1 was assessed with five subtests. These included established measures of immediate and

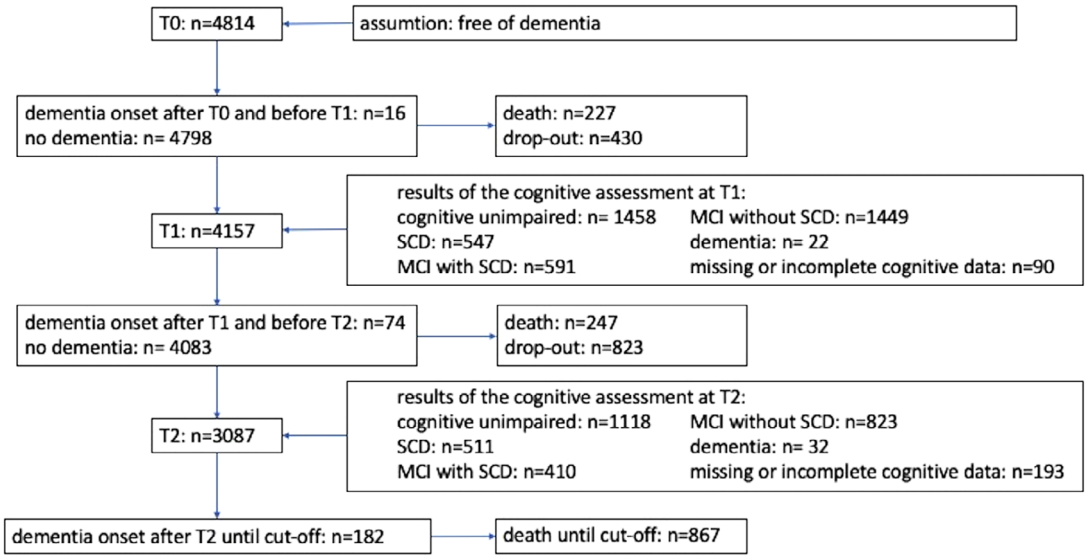

FIGURE 1 Flow-chart of the study population of the Heinz Nixdorf Recall (HNR) study, Germany, from baseline-examination period 2000–2003 until the cutoff of September 1, 2023. MCI, mild cognitive impairment; SCD, subjective cognitive decline; T0, baseline examination; T1, 5-year follow-up examination; T2, 10-year follow-up examination.

delayed verbal memory.[9–11] For a detailed assessment description see Wege et al.[12] Regarding T2, the cognitive performance assessment was extended by the Trail Making Test Parts A and B[13] and a short version of the Stroop task named Color-word test.[14] Of the participants with complete cognitive assessment at T1 ($n = 4067$), 1458 (36%) were cognitively unimpaired, 547 (13%) reported SCD, 591 (15%) had mild cognitive impairment (MCI) and reported SCD, 1449 (36%) had MCI without reporting SCD, and 22 (0.5%) had dementia. Of the participants with complete assessment at T2 ($n = 2894$), 1118 (39%) were cognitively unimpaired, 511 (18%) reported SCD, 396 (14%) had MCI with reporting SCD (including 269 participants with incident MCI and SCD at T2), 823 (28%) had MCI without reporting SCD, and 32 (1%) had dementia.[12,15]

2.3 | Assessment of dementia

We prospectively followed the participants of the HNR study for up to two decades. No cognitive assessment was performed at T0. However, we assume that the participants were without dementia at T0. Incident cases of dementia were detected through annual postal follow-up, in-person examination 5 and 10 years after T0, in given reasons for non-participation, and death certificate research. Further medical reports were requested and dementia cases were validated by an expert committee. In detail, we proceeded as follows.

To identify dementia cases in participants lost to follow-up we started to screen already existing information in our T0, T1, T2, and follow-up database, follow-up questionnaires, medical documents, and death certificates in 2017, for valid information on the dementia status of each participant including those participants who were lost to follow-up. We used the following information: neuropsychological assessment, extended neurological and neuropsychological evaluation in a subset of participants including magnetic resonance imaging (MRI) scans (nested case-control study[12]), follow-up questionnaires, medical reports from general practitioner or neurologist/psychiatrist or hospitalization, medication use, death certificates, and anamnestic information (see SM2 for details).[12,16,17] Anamnestic information was information provided by the participant at the time of the examination, on the follow-up questionnaire, or during the telephone research, as well as information provided by persons who answered our calls during telephone research.

Since T2, annual follow-up and postal questionnaires on health status were continued to obtain information about vital status and to identify new dementia cases. The participants or their relatives or other persons who answered our phone calls were asked about a recent dementia diagnosis, and the medical records of hospitals or physicians for all identified cases were requested. If participants died after the last visit, we identified dementia in the death certificates.

All participants who had been flagged as probable or possible dementia cases according to all available information were further evaluated. The information was presented to the endpoint committee with dementia experts to define dementia and its subtypes as described in detail in the supplements "SM3 Diagnostic criteria of dementia endpoints" and "SM4 Definition of dementia subtypes." We defined the following dementia subtypes: AD (definite/probable/possible), VaD (probable/possible), MD (probable/possible), FTD (probable/possible), LBD (probable/possible), PD dementia, and unspecified dementia.

2.4 | Assessment of *APOE* ε4 status

Cardio-MetaboChip BeadArrays were used for genotyping of two single-nucleotide polymorphisms (SNPs; rs7412 and rs429358) to

distinguish between the *APOE* ε2, ε3, and ε4 alleles. Participants who had at least one allele ε4 were defined as *APOE* ε4 positive, and all others as *APOE* ε4 negative.[15]

2.5 | Assessment of education and vascular risk factors

We determined the following demographic and other baseline characteristics: age, sex, education (self-reported; according to the International Standard Classification of Education[18]), smoking status (self-reported; current [during the past year]/past [quitting >1 year ago]/never), body mass index (BMI, calculated from measured height and weight), diabetes (self-reported; taking antidiabetic medication, measured fasting blood glucose level of ≥200mg/dL or non-fasting level of ≥125 mg/dL (ADVIA 1650, Siemens Healthcare Diagnostics), systolic and diastolic blood pressure (Omron [HEM-705CP], mean from the second and third measurement), antihypertensive medication (self-reported; diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor antagonists, calcium channel blockers, alpha-blockers, centrally active antihypertensive drugs and/or hydralazine intake), total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol (ADVIA 1650, Siemens Healthcare Diagnostics), cholesterol-lowering medication (self-reported), a history of cardiovascular disease and stroke (self-reported), and Agatston score (electron beam CT, GE Imatron).

2.6 | Statistical analysis

Continuous data were represented by mean ± standard deviation (SD) or median and first and third quartile (Q1–Q3) if the distribution was skewed. Categorical variables were represented by frequency (*n*) and percentage (%). It was assumed that participants were not affected by dementia at T0. For this study, we included all incident dementia cases that were identified and validated until September 1, 2023. Among participants with dementia, follow-up time was measured in years from T0 to dementia diagnosis. If the documents indicated that dementia could have been present for some time, we took the earliest known date with dementia. Participants without dementia were censored at the last date on which they were known not to have dementia or at the date of death. Determination of cumulative incidence and incidence rate (IR):

Cumulative incidence: We calculated the cumulative incidence of dementia over a period of two decades (cumulative incidence = number of incident dementia cases per number of observed participants at T0) within strata of sex and age at recruitment (grouped in six age groups from 45 to < 50 to 70–75 years).

Incidence rate$_1$ (IR_1): We calculated the IR per 1000 person-years (py) over a period of two decades (IR_1 = number of incident dementia cases per 1000 py of follow-up) within strata of sex and age at recruitment (grouped in six age groups from 45 to <50 to 70–75 years).

Incidence rate$_2$ (IR_2): We calculated the age-specific incidence within 5-year age groups during follow-up (nine age groups from 45 to < 50 to 85+ years) from person years cumulatively observed in those age groups and age at dementia diagnosis. For this approach, it is assumed that the age-specific incidence did not change between 2000 and 2023.

In SM5 we give an example of how a participant contributes person-years to IR_1 and IR_2. SAS software, version 9.4 (SAS Institute) was used for statistical analyses.

3 | RESULTS

3.1 | Demographic characteristics of the study population at baseline (T0)

Table 1 presents the baseline characteristics of the study population with 4814 participants. Of those, 49.8% were men and the mean age was 59.6 ± 7.8 years. The mean duration of education was 14.0 ± 2.4 years, the mean BMI 27.9 ± 4,6 kg/m^2; 23.4% of the participants were current smokers at T0, and 34.5% reported former smoking.

3.2 | Baseline characteristics of participants with incident dementia compared to no dementia

The cohort was observed for a median time of 18.2 (11.3–20.6) years, and 298 (6.2%) participants developed incident dementia. Of those 155 (52.0%) were male. Sixteen dementias were diagnosed after T0 and before T1; 12 were diagnosed at T1; 74 after T1 and before T2; 14 at T2; and 182 after T2 (Figure 1). In 216 cases (72.5%), medical documents indicated the date of first diagnosis or incipient dementia with a median time to event of 13.1 (10.1–16.1) years. In the remaining 82 cases (27.5%), we selected the earliest known date with dementia. These are, for example, participants with a diagnosis of dementia on the death certificate or a medical report with the diagnosis of severe dementia without details of the onset. As expected, the time to event was slightly higher for this group (data not shown). Participants with incident dementia were older (66.6 ± 5.6 vs 59.2 ± 7.7 years), more often male (50.4% vs 47.8%), had a higher BMI (28.2 ± 4.7 vs 27.9 ± 4.6kg/m^2), had fewer years of education (13.4 ± 2.4 vs 14.0 ± 2.4 years), less often reported current smoking (16.8% vs 23.9%), more often were *APOE* ε4 positive (33.8% vs 19.8%), were more likely to have pre-existing conditions (stroke, diabetes, cardiovascular disease, antihypertensive and lipid-lowering medication intake), had a higher median Agatston score (64.3 vs 16.5) and higher mean blood pressure values, and had a lower mean HDL and higher mean LDL at T0 (Table 1). SM6 presents the baseline characteristics stratified by sex and dementia status over the course. Men with incident dementia had worse cardiovascular profiles at T0 than women (e.g., had more often diabetes and cardiovascular heart disease, higher systolic and diastolic blood pressure, and higher Agatston scores).

TABLE 1 Baseline characteristics of male and female participants 45–75 years of age of the Heinz Nixdorf Recall study, Germany, 2000–2003.

n (%), mean ± SD	Incident dementia	No dementia during follow-up	Total
n	298 (6.2)	4516 (93.8)	4814
Age (y)	66.6 ± 5.6	59.2 ± 7.7	59.6 ± 7.8
Men	155 (52.0)	2240 (49.6)	2395 (49.2)
Women	143 (48.0)	2276 (50.4)	2419 (50.2)
BMI (kg/m^2)	28.2 ± 4.7	27.9 ± 4.6	27.9 ± 4.6
Missing	1	28	29
Education (y)	13.4 ± 2.4	14.0 ± 2.4	14.0 ± 2.4
Missing	1	15	16
Smoking			
Never	155 (52.0)	1858 (41.1)	2013 (41.8)
Former	92 (30.9)	1569 (34.7)	1661 (34.5)
Current	50 (16.8)	1078 (23.9)	1128 (23.4)
Missing	1 (0.3)	11 (0.2)	12 (0.2)
***APOE ε4* positive**	101 (33.8)	895 (19.8)	996 (20.7)
Missing	49 (16.4)	876 (19.4)	925 (19.2)
Stroke	15 (5.0)	120 (2.7)	135 (2.8)
Missing	2	27	29
Type 2 diabetes	52 (17.4)	603 (13.4)	655 (13.6)
Cardiovascular disease	29 (9.7)	298 (6.6)	327 (6.8)
Missing	1 (0.3)	14 (0.3)	15 (0.3)
Median Agatston score (Q1;Q3)	64.3 (2.8; 380.6)	16.5 (0; 152.7)	18.3 (0; 166.1)
Missing	8	228	236
Systolic blood pressure (mmHg)	138.3 ± 21.7	132.8 ± 20.8	133.1 ± 20.9
Missing	1	14	15
Diastolic blood pressure (mmHg)	81.6 ± 11.5	81.4 ± 10.8	81.4 ± 10.9
Missing	1	13	14
Antihypertensive medication	132 (44.1)	1498 (33.2)	1630 (33.8)
Missing	25 (8.4)	296 (6.6)	321 (6.7)
HDL (mg/dL)	57.7 ± 15.5	58.0 ± 17.3	58.0 ± 17.2
Missing	0	24	24
LDL (mg/dL)	148.1 ± 36.5	145.3 ± 36.2	145.5 ± 36.2
Missing	0	37	37
Lipid-lowering medication	55 (18.4)	539 (11.9)	594 (12.3)
Missing	24 (8.0)	290 (6.4)	314 (6.5)

Abbreviations: *APOE*, apolipoprotein E; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Q1, lower quartile; Q3, upper quartile; SD, standard deviation; y, years.

3.3 | Dementia subtypes

Table 2 shows the subtypes of the 298 incident dementia cases; 66 (22.1%) had AD, 70 (23.5%) VaD, 45 (15.1%) MD, 1 (0.3%) FTD, 2 (0.7%) LBD, and 24 (8.1%) PD dementia. In 90 cases (30.2%), insufficient information was available for subtype classification (unspecified dementia). The proportion of unspecified dementia was lower in men than in women (25.2% vs 35.7%). The mean age at dementia onset of the participants with unspecified and specified dementia was similar (data not shown). FTD and LBD were present only in men.

3.4 | Cumulative incidence and incidence rate by age group and sex

*Table 3 shows the mean age at dementia onset, the cumulative incidence, and the IR per 1000 person-years of dementia by age group and

TABLE 2 Diagnostic criteria and subtypes of incident dementia cases; *n* (%).

Definite **Alzheimer's disease dementia**	**6**	**Total: 66 (22.1);** men: 35 (22.6) women: 31 (21.7)
Diagnosis in medical reports	6	
Diagnosis on death certificate	0	
Evidence for amyloid and tau	6	
Marker for neuronal damage (A+/T+/N+)	2	
Probable **Alzheimer's disease dementia**	**43**	
Amyloid markers present only	0	
Markers of neuronal damage present only (AD specific)	19	
Diagnosis in medical records	28	
Diagnosis on death certificate	10	
Possible **Alzheimer's disease dementia**	**17**	
Markers of neuronal damage present (not AD specific)	6	
Statement about cognitive dysfunction	9	
Acetylcholinesterase inhibitors or memantine intake	9	
Probable **mixed dementia**	**17**	**Total: 45 (15.1);** men: 26 (16.8) women: 19 (13.3)
Criteria for definite or probable Alzheimer's dementia are fulfilled (see above)	17	
Evidence of vascular pathology	17	
Possible **mixed dementia**	**28**	
Diagnosis in medical records	25	
Diagnosis on death certificate	3	
Probable **vascular dementia**	**37**	**Total: 70 (23.5);** men: 39 (25.2) women: 31 (21.7)
Presence of Major Neurocognitive Disorder	17	
Diagnosis in medical records	20	
Diagnosis on death certificate	8	
Evidence of a vascular etiology of cognitive impairment	34	
Possible **vascular dementia**	**33**	
Statement about cognitive dysfunction	13	
Cognitive dysfunction and multiple cardiovascular risk factors	33	
Diagnosis on death certificate	2	
Possible **frontotemporal dementia** Diagnosis on death certificate	**11**	**Total: 1 (0.3);** men: 1 (0.6)
Probable **Lewy body dementia** Diagnosis in medical records	**22**	**Total: 2 (0.7);** men: 2 (1.3)
Probable **Parkinson's disease dementia**	**9**	**Total: 24 (8.1);** men: 13 (8.4) women: 11 (7.7)
Diagnosis of Parkinson's disease	9	
Diagnosis of dementia that has developed with Parkinson's disease	9	
Typical cognitive deficits in at least two domains	9	
Behavioral characteristics	6	
Possible **Parkinson's disease dementia**	**15**	
Both core features are present, but cognitive profile is typical, or not enough domains are affected or one of the first two exclusion criteria are met, and the last three exclusion criteria must not be met	4	
Diagnosis in medical records or a combination of any dementia diagnosis and Parkinson's diagnosis	9	
Diagnosis on death certificate	5	

(Continues)

TABLE 2 (Continued)

Unspecified dementia	**90**	**Total: 90 (30.2);** men: 39 (25.2) women: 51 (35.7)
Unspecified dementia diagnosis in medical records	28	
Unspecified dementia diagnosis on death certificate	33	
Unspecified dementia recorded in documents without additional information	25	
Dementia diagnosis at cognitive assessment at T1 or T2 without additional information	15	
		Total: 298 (100); men: 155 (100) women: 143 (100)

Abbreviations: AD, Alzheimer's disease; T1, first follow-up examination; T2, second follow-up examination.

TABLE 3 Cumulative incidence and incidence rate per 1000 person-years of dementia by age group and sex over a period of 20 years in participants of the Heinz Nixdorf Recall study, Germany, baseline examination 2000–2003.

Age at T0 (y)	*n*	py of follow-up (y), median (Q1-Q3)	Incident dementia (*n*)	Age at dementia onset (y, mean ± SD)	p until dementia, median (Q1-Q3)	Cumulative incidence (%)	IR_1 per 1000 py
Men							
45 to <50	307	19.77 (13.44–20.95	1	64.81	15.81	0.33	0.19
50 to <55	439	19.82 (13.37–20.89)	5	70.04 ± 5.87	17.83 (16.10–18.97)	1.14	0.66
55 to <60	399	19.39 (14.68-20.76)	9	71.41 ± 6.82	13.90 (11.72–16.19)	2.26	1.32
60 to <65	541	18.00 (11.30–20.57)	41	75.42 ± 5.21	16.65 (10.06–16.65)	7.58	4.77
65 to <70	406	15.35 (9.61–19.25)	47	79.46 ± 4.11	12.84 (10.15–16.45)	11.58	8.17
70–75	303	11.23 (7.56–15.89)	52	82.88 ± 4.41	10.70 (7.77–14.30)	17.16	14.91
Total	**2395**	**18.06 (11.01–20.64)**	**155**	**78.67 ± 6.13**	**12.61 (8.93–16.14)**	**6.47**	**4.13**
Women							
45–<50	303	20.42 (17.84–20.99)	3	60.06 ± 3.98	10.82 (10.20–16.15)	0.99	0.54
50 to <55	445	19.92 (15.55–20.89)	2	65.81 ± 3.70	12.31 (10.19–14.43)	0.45	0.13
55 to <60	425	19.52 (15.31–20.80)	15	73.70 ± 3.84	17.15 (14.21–18.28)	3.53	2.04
60 to <65	532	18.12 (11.81–20.46)	22	76.04 ± 3.82	14.10 (11.26–15.84)	4.14	2.54
65 to <70	407	16.47 (10.57–19.70)	41	80.36 ± 4.28	13.40 (10.33–16.43)	10.07	6.64
70–75	307	12.22 (9.26–16.52)	60	84.14 ± 4.29	12.55 (10.23–15.49)	19.54	15.49
Total	**2419**	**18.57 (11.72–20.67)**	**143**	**79.95 ± 6.47**	**13.35 (10.44–16.15)**	**5.91**	**3.63**
Total	**4814**	**18.19 (11.34–20.65)**	**298**	**79.29 ± 6.32**	**13.06 (10.13–16.14)**	**6.19**	**3.87**

Abbreviations: IR_1, incidence rate per 1000 py over a period of 20 years; py, person-years; Q1, lower quartile; Q3, upper quartile; SD, standard deviation; T0, baseline; y, years.

sex over a period of two decades (IR_1). As expected, older participants at T0 had a higher cumulative incidence of dementia. In addition, the mean age at dementia onset was higher in the older age groups. The mean age at dementia onset was slightly lower in men compared to women (78.67 ± 6.13 vs 79.29 ± 6.32 years) and the IR_1 was slightly higher in men (4.1 vs 3.6 per 1000 py). The cumulative incidence and IR_1 were highest among women 70–75 years at T0 (20%, 15.5/1000 py). Men that age had a slightly lower cumulative incidence and IR_1 (17%, 14.9/1000 py).

Figure 2, Figure 3, and SM7 show the IR per 1000 person-years of dementia in men and women per age group (IR_2) and the distribution of years at the onset of dementia (SM8 for the total cohort). In 10 participants, dementia began at <65 years of age and in 3 participants at <60 years of age. The IR_2 in the 55 to <60, 60 to <65, 65 to <70, and 70 to <75 year groups in Figure 2, Figure 3, and SM7 are lower than in Table 3, which represents an age cohort over a 20-year period. For example, men 70 to <75 years had an IR_1 of 15.49 and an IR_2 of 3.83 per 1000 person-years, because many younger participants were observed for many years until few of them developed dementia, and many younger participants were not observed long enough to develop dementia at all. On the other hand, many persons were followed far beyond the range of recruitment age (which was limited at 75 years), allowing for additional higher age groups in Figure 2, Figure 3, and SM7, with many cases diagnosed.

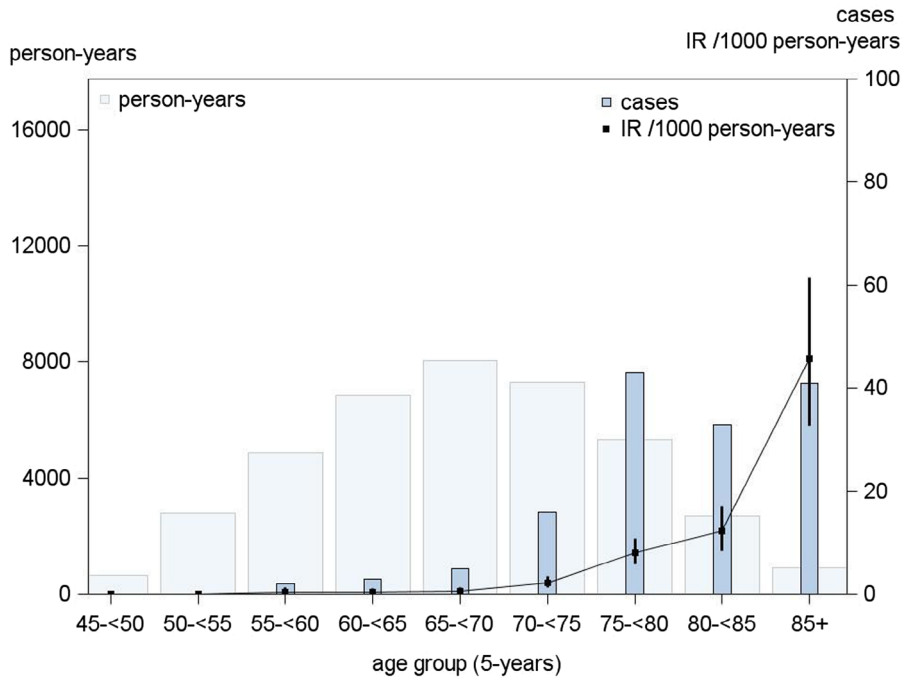

FIGURE 2 Age-specific incidence rate per 1000 person-years of dementia per age group (IR_2) and distribution of observed person-years and cases diagnosed with dementia per age group in **male** participants of the Heinz Nixdorf Recall study, Germany, baseline examination 2000–2003.

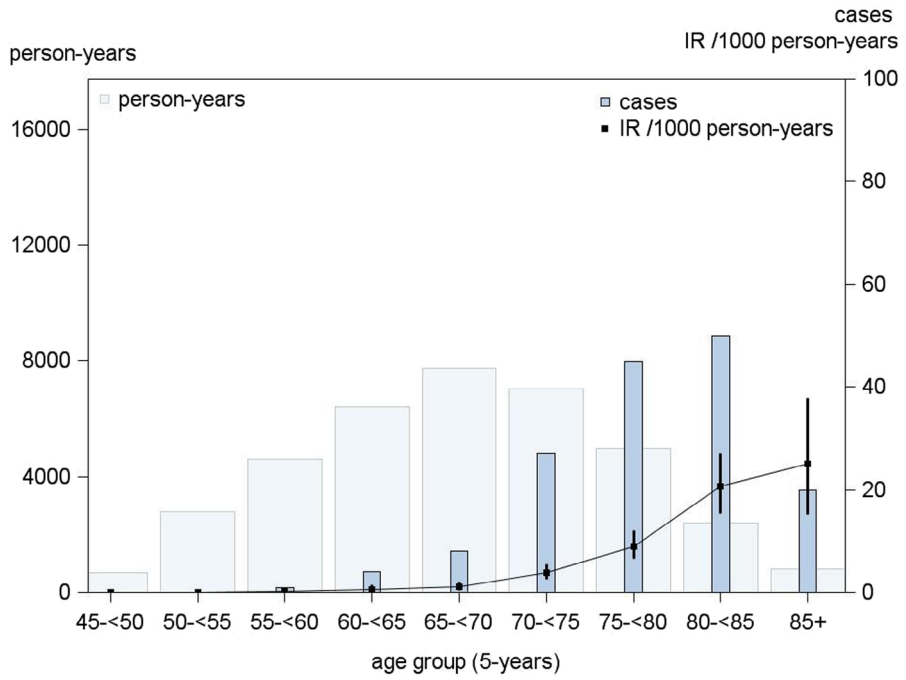

FIGURE 3 Age-specific incidence rate per 1000 person-years of dementia per age group (IR_2) and distribution of observed person-years and cases diagnosed with dementia per age group in **female** participants of the Heinz Nixdorf Recall study, Germany, baseline examination 2000–2003.

4 | DISCUSSION

For two decades we prospectively followed a large cohort from the general German population, which was expected to be free of dementia at T0. New cases of dementia were detected through annual postal follow-up, in-person examination 5 and 10 years after T0, in given reasons for non-participation, and death certificate research. Further medical reports were requested and dementia cases were validated

by an expert committee. Age-specific dementia incidence rates were estimated.

Of 4814 participants 45–75 years at T0, we identified 298 incident dementia cases (6.2%) after a median follow-up of 18.2 (11.3–20.6) years with a mean age at onset of dementia of 79.3 ± 6.3 years. Of those cases, 155 (52.0%) were male. Sixty-six participants (22.1%) had AD, 45 (15.1%) MD, 70 (23.5%) VaD, 1 (0.3%) FTD, 2 (0.7%) LBD, and 24 (8.1%) PD dementia. FTD and LBD were present only in men. Of the participants with a specific dementia diagnosis, ≈60% had AD or MD. In 90 cases (30.2%), insufficient information was available for a more specific dementia classification. This could indicate that we did not have all the available documents for a more specific diagnosis. It could also imply that a considerable proportion of patients with dementia did not receive a more precise diagnosis. In two-thirds of those cases, we could not provide a more specific diagnosis, although medical reports or death certificates were available. This illustrates that even in medically highly developed industrialized countries such as Germany, a sufficient dementia diagnosis work-up is not available and accessible to everyone.

We observed sex differences in our study. The IR over a period of two decades was slightly higher for men than for women (4.1 vs 3.6 per 1000 py). Dementia was diagnosed somewhat earlier in men than in women (age at dementia onset: 78.67 ± 6.13 vs 79.95 ± 6.47 years). Men with incident dementia had worse cardiovascular profiles at T0 than women, and the proportion of unspecified dementia was lower in men than in women (25.2% vs 35.7%). A direct sex comparison of the dementia subtypes is therefore not meaningful. Studies in Europe showed inconsistent results, reporting higher incidence among women at older ages[19,20] or higher incidence among men.[21] There is evidence that observed differences in dementia incidence between men and women may be artificial and due to other risk factors before developing dementia.[22] It might be that the poorer cardiovascular profile in our male study population, especially when conditions were treatable, has led to an earlier medical examination, where any cognitive impairment may also have become apparent. Furthermore, there is a difference in dementia caregivers. As two-thirds of dementia caregivers are women and women show more preventive health behavior, they might persuade their men to have health check-ups.[23–26] That might also in part explain the younger age at diagnosis in our male participants with dementia. That in turn might have resulted in lower unspecified dementia rates by in-depth examinations to rule out treatable conditions at younger ages. In Germany, biomarker testing (especially cerebrospinal fluid biomarkers) is unusual in an outpatient setting. If dementia is diagnosed at an advanced age, caregivers often do not want further clarification in order to spare the patient a hospital stay, especially because there is no causal treatment. However, further studies are needed to clarify possible sex differences in different care settings.

Previous cohort and register studies investigated the dementia incidence in Europe and the United States with heterogeneous results. Dementia onset before the age of 65 years is scarce.[27,28] Most studies examined participants ≥65 years of age at baseline. Our cohort also included younger participants (age at T0: 45–75 years), and we were able to identify some cases with early dementia onset: three dementia cases in the age group 55 to <60 years with an IR_2 of 0.22/1000 person-years in men and 0.41/1000 person-years in women; and seven cases in the age group 60 to <65 years with an IR_2 of 0.62/1000 person-years in men and 0.44/1000 person-years in women. Due to methodological differences, the IR of our subjects in the younger age groups is difficult to compare with the previous literature.[27,28] The Alzheimer Cohorts Consortium reported the dementia incidence of seven population-based long-term cohort studies from Europe and United States between 1988 and 2015.[29] The IR per 1000 person-years per age group ranged as follows: 65 to <70 years: 2.3–10.9 in men, 1.6–6.4 in women; 70 to <75: 7.0–19.2 in men, 5.7–19.7 in women; 75 to <80: 11.8–43.5 in men, 13.4–33.4 in women; 80 to <85: 19.3–57.1 in men, 29.0–58.6 in women; and 85 to <90: 37.7–118.9 in men, 45.8–89.2 in women. Regarding our IR_1 estimates, those studies provide results that are comparable to our study for only the groups 65 to <70 and 70 to <75years. Our estimates of IR_1 for the group 65 to <70 (4.8 in men, 2.5 in women) and 70 to <75 years (6.6 in women, 8.2 in men) were within these ranges. Our IR_2 estimates were generally lower. Because our IR_2 estimates represent age-specific IR, they are more comparable with IR obtained from registry studies. However, our IR_2 was calculated from data over a much longer calendar period than is usually done for registry data. A Swedish registry study from 1987 to 2016, reported IR per 1000 person-years that was comparable to our IR_2: 65 to <70 years: 0.84 in men, 0.73 in women; 70 to <75: 2.41 in men, 2.16 in women; 75 to <80: 6.15 in men, 5.75 in women; 80 to <85: 12.46 in men, 12.29 in women; 85 to <90: 21.30 in men, 21.15 in women; and 90 to <95: 27.81 in men, 28.05 in women.[30] There were fewer people in the very old age groups in both our study and the registry study. This could be the reason for the difference in IR here. In addition a Danish registry study from 1996 to 2015[31] and the Tromsø study in Norway from 2000 to 2019[32] reported similar IRs. Our IR agrees well with previous findings in population-based cohort studies and registry studies. In addition, our study also provides estimates for younger age groups.

Difference in dementia incidence rates might also vary due to social, cultural, and economic experiences, even in the same country.[33] In the United States, the risk of dementia appears to vary by race and ethnicity.[34,35] Most studies indicate that Black older adults are about twice likely to have Alzheimer's and other dementias as White older adults.[36,37] Research suggests that disparities in life experience, socioeconomic factors, and, ultimately, health conditions most likely explain the difference in risk for Alzheimer's and other dementias among racial and ethnic groups.[38] This is also true for low- and middle-income countries. Although a growing number of studies indicate that the prevalence and incidence of Alzheimer's and other dementias have declined in high-income countries over the past 25 years, there is not such a trend for low- and middle-income countries.[29,39,40] A comparison of the incidence of dementia between different countries with different socioeconomic statuses and health systems and therefore different individual health statuses is especially challenging, however, necessary, because the number of people 65 years of age and older with Alzheimer's dementia is projected to reach 13.8 million (solely in the United States) by 2060, with an immense impact on

the health care system including caregivers.[23] Recently, 14 modifiable risk factors were shown to account for ≈45% of worldwide dementias, which consequently could theoretically be prevented or delayed.[22] The potential for prevention is high and might be higher in low-income and middle-income countries, where more dementias occur most likely due to lower levels of education and higher cardiovascular morbidity. Germany is a high-income country with a high level of education. Due to our study inclusion criteria (German citizenship, good German language skills), only middle-aged and older White adults with a homogeneous cultural background participated in our study. Our results are representative of this group.

Our data show that dementia represents a relevant health burden and that the diagnosis of dementia must be improved in Germany, preferably at an early stage. The underdiagnoses of dementia might lead to delayed access to treatment, less time for care planning, and higher costs for care, and have a negative impact on the physical or mental health of patients and caregivers.

The strengths of our study are that we included participants at the age of 45 years and followed participants over two decades. Our study provides a broad overview of the course of dementia over time and differs from other studies with a usually shorter follow-up. Another strength is the high data quality. The HNR study was certified in the years 2000 and 2008 (DIN EN ISO 9001:2000/2008), and it follows a strict study protocol. Data were subject to stringent quality control and protection. A limitation of our study is that no cognitive assessment was performed at T0. We only assume that the participants were without dementia at T0, because first-time participation in such a comprehensive study with an examination time of ≈6 h is not very likely for people with dementia. However, it cannot be completely ruled out that there were still participants with incipientdementia at T0. Another limitation is that the decline of cognitive abilities after the participants' last visit to our study center may have occurred at different rates. It was difficult to define the exact time of onset of dementia. A major limitation (compared with clinical studies) is that our dementia diagnosis is mostly based on clinical and neuroimaging data, but not on cerebrospinal fluid or positron emission tomography biomarker information. Various methods were used to detect dementia in our study population, and the accuracy of medical records and documentation was heterogenous. Yet, this lack of information represents the current stage of dementia diagnosis in the general population in Germany. Medical records in Germany only have to be kept for 10 years; therefore it may not always have been possible to provide us with all the documents. In some cases, doctors or hospitals refused to send us medical records, or no suitable medical facility could be contacted. So there is certainly a bias in the recording of dementia and also a certain bias in dropping out of the study. However, a certain degree of uncertainty in the diagnosis is common in epidemiological studies.[1,32,41] Due to the high-response proportion of our participants as well as the possibility to request many medical records and death certificates, we believe that in most cases we found out whether participants developed dementia or not. Our approach is state-of-the-art in population-based studies.

5 | CONCLUSIONS

We identified incident dementia cases in a population-based study over a period of two decades. Our estimates of dementia incidence were comparable to those of previous studies in Europe and the United States, and are representative of the middle-aged and elderly German population. The overall IR after a median follow-up of 18.2 (11.3–20.6) years of the cohort with balanced sex distribution and a mean age of 59.6 ± 7.8 years at T0 was 3.9/1000 person-years. The mean age at dementia onset was 79.3 ± 6.3 years. Dementia seemed to be diagnosed somewhat earlier in men than in women. Further specification of the dementia subtype was possible in ≈70% of the cases (22.1% of participants developed AD, 23.5% VaD, 15.1% MD, and 9.1% other dementia). In around 30% of the cases, dementia could not further be specified. The reason may be that we did not have enough information due to possibly incomplete research, but it is more likely that a large proportion of these patients did not undergo intensive diagnostic work-up and did not receive a more precise diagnosis. The diagnosis of dementia urgently requires improvement in the near future. Efforts should be made to carry out an accurate and early diagnosis using currently established tests. Further diagnostic tests, in particular blood-based biomarker diagnostic, must be developed for broadly applicable and cost-effective diagnosis.

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CONFLICT OF INTEREST STATEMENT

All authors declare that they have no competing interests or conflicts. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

The authors confirm that all participants of the study provided informed consent.

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SUPPORTING INFORMATION

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